



May 7, 2021

Marietta Echeverria, Acting Division Director
Registration Division
Office of Pesticide Programs
United States Environmental Protection Agency

Dear Ms. Echeverria,

Elanco is hereby providing a description of the information that we intend to submit in response to the letter received April 27, 2021, "Subject: Information Concerning Seresto Collars That Must Be Reported Pursuant to FIFRA section 6(a)(2)." We provide below the requested description of information that will be submitted in response to Items 1 through 8 in the April 27 letter, as well as material that will be provided in response to the un-numbered request in said letter. The information that we will submit is supplemental to the significant amount of data provided to the Agency related to the Seresto collars since the product's registration in 2013, including that presented by Elanco on March 23 and April 6, 2021.

1. Any information concerning the annual incident rate (e.g., incidents per million units sold) for Seresto collars stratified by clinical severity including, if available, by collar size/type (e.g., cat, small dog, large dog). Provide any supporting data, and criteria used to develop this response, in addition to any calculations (e.g., Reporting Odds Ratios (ROR) or Incident Rate Ratios (IRR)) that Elanco may have performed to address this question.

Elanco will provide:

- A table with incident rates since 2013 by severity categories (D-A, D-B, etc.) including number of cases and collars distributed
- A table with incident rates for 2020 for all Preferred Terms above 1/10,000 (showing number of cases and collars distributed)
- A detailed report with disproportionality analysis background and Elanco's data analysis approach

- A graphic with data and calculations of Incident Rate Ratio for Seresto and K9 Advantix II based on pet month of protection

2. Any information concerning the adverse reactions/advisories that are listed on the Seresto collars labels in the European Union and their prevalence, including any supporting data that was reviewed by EU regulatory authorities to determine that these adverse reaction could happen and are rare/very rare cases (based on frequency of adverse reactions per 10,000 collars sold).

Elanco will provide the current EU labels including adverse reactions and frequencies for the different product presentations. Additionally, Elanco will provide information provided to EU authorities by means of Periodic Safety Update Reports (PSURs). Specifically, Elanco will provide the following:

- PSUR ID 60793: Summary Bridging PSUR for European Economic Area (EEA), covering one pre-launch PSUR and five post-launch PSURs for the period 27 July 2011 to 31 January 2015
- PSUR ID 60807: Second 1-year PSUR for EEA for the period 01 February 2015 to 31 January 2016
- PSUR ID 61087: First 3-year PSUR for EEA for the period 01 February 2016 to 31 January 2019

3. Any information concerning your global pharmacovigilance program for Seresto collars and other veterinary medical products, including a summary of any specific pharmacovigilance activities that have been performed by Elanco on suspected adverse reactions in the U.S. and other major global markets. The summary must include information on reported adverse reactions to Seresto collars, analysis of the incident rate of more serious adverse reactions, and investigation of specific clinical signs that have been identified as potential safety signals of concern by global regulatory authorities. Additionally, should include existing comparative analysis of Seresto collars and related pet products that marketed by Elanco and part of its global pharmacovigilance program.

Elanco will provide:

- A description of Elanco's global post-market-surveillance system covering the end-use product Seresto collar, as well as relevant key standard operating

procedures

- Safety Management Team (SMT) meeting minutes related to Seresto which document internal, cross-functional team evaluation of any safety signals identified globally by either the company or regulatory authorities
- The internal investigations of US Seresto incident reports and independent third-party case reviews by Safety Call International and KNW Animal Health Consulting
- Furthermore, the comparative analysis of Seresto collars and related pet products that will be submitted in response to Item 1 and to the PSURs which will be submitted in response to Item 2 also contain information relevant to this request

4. All available sales data and detailed/enhanced incident data for Seresto collars. Please provide the incident information, in electronic format, using the EPA's spot-on reporting templates (<https://www.epa.gov/pesticides/use-standardized-templates-report-pet-spot-incidents-conclusion-pilot-and-implementation>).

On August 28, 2015, Elanco submitted the enhanced reporting data for Seresto from product launch through June 30, 2015. In response to this request, Elanco will provide sales and incident data from July 1, 2015 through year end 2020. As the request indicates Elanco should provide the information using the EPA's spot-on reporting templates, the incidents will be provided using the existing Legacy Bayer Animal Health output for enhanced reporting for the Legacy Bayer Animal Health spot-on products.

5. All available pre-market data for Seresto collars that has not previously been submitted (e.g., FDA requirement Guideline No: 85 (VICH GL9)).

Elanco will provide all studies evaluating the safety of the end-use product Seresto collar as conducted for global registrations including assessments of target animal and user safety.

6. All information concerning incident analyses, including supporting data/incident reports, that has been previously shared with PMRA or other regulatory bodies.

Elanco will provide data submitted to PMRA in response to their questions

regarding the initial request for registration (2016) and as part of recent registration activities (2019).

Furthermore, the PSURs that will be submitted in response to Item 2 and the SMT meeting minutes that will be submitted in response to Item 3 also contain information relevant to this request.

7. *All information concerning the underlying data supporting your own analyses of the incidents, including those analyses on neurological effects.*

Elanco will provide documentation demonstrating that the reports Elanco has received related to serious neurological disorder and death are not related to the active ingredients in Seresto. These documents support the Weight of Evidence analysis that was shared on Slides 40 and 41 at the meeting held on April 6, 2021.

This will include:

- Incident rate analysis including disproportionality analysis and incident rate ratios
- Line listing of the 12 death reports assessed probable (A) or possible (B) product related by Elanco (in the US from launch to end April 2021) and a third- party case review by KNW Animal Health Consulting of the same
- Line listing of the 23 convulsion reports assessed probable (A) or possible (B) product related by Elanco (in the US from 01 Jan 2020 through 31 Dec 2020)
- Line listing of case reports after chewing and/or ingestion of the collar (in the US for 2020)
- Reference to relevant toxicological, kinetic and Target Animal Safety / Companion Animal Safety study reports
- Literature references on background prevalence of convulsions in dogs
- For the Agency's convenience, Elanco will re-submit to the EPA our perspectives on PMRA's human and animal incident assessments, originally provided to the Agency via email on August 19 and September 2, 2016,



respectively

- “Seresto Review of PMRA Assessment,” an expert report compiled by Cyton Biosciences which is complimentary to the perspectives on PMRA’s human and animal incident assessments referenced above
- A “Seresto White Paper” compiled by Cyton Biosciences

Furthermore, the PSURs which will be submitted in response to Item 2 and the internal investigations of US Seresto incident reports and independent third- party case reviews by Safety Call International which will be submitted in response to Item 3 also contain information relevant to this request.

Finally, in addition to standard internal evaluation of adverse event data for signal detection as well as earlier external, third-party assessments conducted as an additional review, Elanco has commissioned the following: 1) an external case review by KNW Animal Health Consulting of reported deaths and 2) a report regarding Pet Poison Helpline experience with Seresto case reports. This work has been initiated and the results will be shared once available.

8. Any reports and supporting information, including incident and market data, to support the following assertions made by Elanco and its representatives during the March 23, 2021 meeting, convened between Elanco and EPA convened to discuss Elanco’s review of the safety profile of Seresto collars:

- a. From 2013-2020, the overall annual rate of reported incidents has decreased while the number of Seresto collars distributed in the U.S. has increased***

Elanco will provide a report with the data supporting the generation of the chart shared on Slide 8 during the March 23, 2021 meeting.

- b. Based on causality assessment of pet deaths reported during 2013-2020, there is no established link between death and exposure to the active ingredients in Seresto collars.***

Elanco will provide information about the investigation of US data providing support to this statement. Furthermore, the information provided for Item 7 supporting the respective Weight of Evidence analysis also contains information relevant to this request.



- c. The incident rate of reported neurological signs in pets is “very rare” and may reflect the background prevalence of seizures/convulsions in pets.***

Elanco refers to the responses for Items, 1, 2 and 7 which address this Item (8c).

In addition, when assessing the reported incidents, EPA intends to compare the rates of incidents for comparable products. To assist that comparison EPA requests you provide incident rates for your other pet products, including the Advantage II and K9 Advantix product lines.

Elanco has previously submitted the incident and sales information for the Advantage II and K9 Advantix II products through the enhanced reporting process. The last submission contained data for 4Q2019 and was received by the Agency on February 28, 2020.

In April 2020, the Agency's front office was temporarily closed due to the COVID-19 pandemic. Elanco was notified that hard copy 6(a)(2) submissions should be held until the office reopened. Elanco has notified the Agency, as directed, via email to the appropriate Product Managers when the reports are completed each quarter.

Elanco will provide the enhanced incident and sales information for the Advantage II and K9 Advantix II products for 2020 in response to this Item.

Elanco intends to provide these documents on or prior to May 26, 2021 via CDX as agreed during our call on May 4, 2021 and subsequent follow-up emails.

We are confident that this information, in addition to what we have already discussed and provided, further substantiates the strong safety profile of the Seresto collar – particularly given the important protection the product provides to dogs and cats from fleas and ticks.



Respectfully submitted,

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